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Modern Advances in Therapeutics

by

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Advance in the treatment of disease during the present century has been phenomenal. Probably only those of us who have witnessed and lived through this progress since the early years of the century can appreciate its full extent and significance. When I was a medical student doing clinical work in the years 1907-10, I constantly wondered at the attitude of my clinical teachers towards individual cases in hospital. Infinite pains were taken to diagnose the illness, and teaching at the bedside of diagnosis was very thorough. This was excellent. But after the diagnosis was made, I looked forward to learning the proper treatment of the condition. To my surprise, the physician either passed on to the next case without mentioning the subject, or in a perfunctory manner issued a few orders to the house physician and left the case. There was no teaching, on what I thought ought to have been the main object of the physician, namely to cure the patient. Only slowly did I understand this method of procedure, but looking back it is clear that his omission to discuss treatment was only too often due to the fact that there was no adequate treatment for these sick people. In many cases the physician said with a smile that this was a case for 'expectant treatment'—clearly an expression of hope that having diagnosed the complaint, Nature would play her part and cure the patient. Nature fortunately often rose to the challenge and cured the patient but this was by no means always the case.

In those days most drugs were given in order to remove symptoms: morphine to relieve pain, expectorants to relieve cough, purgatives to stimulate the alimentary canal, tonics like strychnine and arsenic to rouse the sluggish body, sedatives like potassium bromide to soothe the nerves, digitalis to quieten the heart, sodium carbonate to relieve dyspepsia. It is undoubted that some of the drugs in use were of real value, some were useless and some were probably harmful. Many of these drugs continue to be used to this day and we would be sorely tried if we had not such substances as digitalis, morphine, cocaine and the saline purgatives. I want to make it clear that symptomatic treatment of disease is still of great importance and will continue to be so whatever may be the advance in therapeutics. Not many drugs at that time were given which dealt with the cause of the disease although there were a few such, including quinine in malaria, ipecacuanha (but not emetine) in dysentery, mercury and iodide in syphilis. But this was more or less an accident because all these drugs had long been in use before the discovery of the malaria parasite and before the recognition of the part played by the Entamoeba hystolytica in dysentery, and the spirochaete in syphilis. Indeed, this class of curative drugs had been discovered empirically by past generations of medical men who neither knew the real nature of the disease they were treating, nor the way the remedy acted. By hit and miss methods throughout the

generations, they had made those valuable discoveries, for which we must be very grateful.

All the drugs I have so far mentioned were substances foreign to the human body. There was, however, just beginning in the early part of the century, thanks to the development of physiology and bacteriology, an appreciation that the administration of substances naturally present in the body was very useful in some diseases. Good examples of this are the treatment of cretinism and myxoedema by thyroid gland, and that of diphtheria by diphtheria anti-toxin. The significance of both of these forms of treatment was that, unlike symptomatic treatment, they dealt with the cause of the disease and opened up new forms of therapy, hormonal and immunological respectively, which have been greatly developed in modern times and have revolutionised treatment of many diseases.

I hope this brief statement of what I actually experienced as a medical student is a, not unreasonable, view of therapeutics up to about 1910. The impetus which began then has grown with the passing of years until now we all have difficulty in keeping pace with the advances made. Before dealing with this question of modern progress, I should first like to pay tribute to the physicians of the nineteenth century, as it might be assumed from what I have said on the undeveloped nature of the subject and the inadequacy of the treatment of disease before and early in the present century that they were open to criticism. It is perfectly clear that modern work on therapeutics could have made no progress had we not had reasonably good knowledge of the classification and nature of disease. The physician of the 19th century studied disease according to his own simple observational methods in a most thorough way, not only at the bedside but, in case of death, at the postmortem. In this way we got all our basic knowledge of the signs, symptoms and, in general, of the natural history of many specific diseases, and this was the essential foundation for subsequent progress.

What in a word has been the import of our recent advancement in therapeutics? Well, it is the discovery of drugs which act on the causal agents of disease and do not act primarily as relievers of symptoms. It has depended on advance in knowledge of many branches of medicine, of physiology, pathology, bacteriology, and of biochemistry. So important have been the chemotherapeutic discoveries in recent years that we are apt to think that the chemist alone has been the determining factor in this advance, but let us not forget that the chemist would have been completely ineffective had he not had the biologist (in the widest sense) and the physician as his allies. The progress, has, indeed, depended on the constantly greater use of the experimental method, the most important discovery that the human mind has yet used and developed.

Let us now try to get a balanced view of what is desirable when dealing with disease. It is necessary to say a few words on this point because the present appraisal among ordinary people and, indeed, among many medical scientists and doctors themselves seems to me to be wrong. What the public like and what brings about the greatest kudos and approval is the discovery of a drug which converts a man doomed to death back to health. It does not matter whether the drug cures pneumonia or a general septicaemia in a few days or just keeps a man or woman well by constant administration of the remedy as in the case of insulin in diabetes or liver extract (or B_{12}) in pernicious anaemia. These are regarded as the greatest achievements. But is this so? Surely our primary object must be to prevent and, if possible, to eliminate disease. Discoveries which lead to this ideal situation do not usually receive much public acclaim because with the elimination of the

disease it is forgotten, and the procedure which leads to it becomes a part of routine practice and is also forgotten. These discoveries are usually of a fundamental nature which illuminate the actual cause of diseases and bring more new knowledge of the physiology and pathology of the body. They are generally concerned with microbiology and its offspring immunology or with the hormonal control of the body or its metabolic or nutritional requirements. I need only remind you of the prevention of small-pox by vaccination, of diphtheria by diphtheria toxoid, of typhoid fever by typhoid vaccine, of rickets, scurvy, beri beri and pellagra by the specific dietetic factors in each disease, of goitre and simple anaemia by iodine and iron respectively. These are the vital discoveries in preventive medicine. I emphasize the point at this stage because of the greater acclaim of modern discoveries in chemotherapy and antibiotics. In lectures on therapeutics, all discussion is now centred on these remarkable advances and I also shall follow this line by spending the rest of this discourse in discussing chemotherapeutic and related discoveries. At the same time I am anxious to leave no doubt in the mind of my audience that the discovery of modern curative drugs is secondary to those discoveries which lead not only to the cure but also to the prevention and elimination of disease.

The development of Chemotherapy:

Ehrlich was the father and initiator of this wonderfully successful form of medical treatment. After playing a great part in developing knowledge of anti-toxins and antigens, you will remember that he decided that this form of study held out no hope for the treatment of some diseases such as malaria. Ehrlich thought that on the analogy of quinine, remedies might be found for infective conditions, including malaria, along chemical lines by substances foreign to the body. He became specially interested in the staining qualities of aniline dyes and studied particularly the affinity of the malaria parasite for methylene blue, a dye which was not very toxic to the host. Although methylene blue was inferior to quinine in the treatment of malaria, these experiments really initiated the subject of chemotherapy. It is of interest to note that when, after many years, a better chemotherapeutic remedy for malaria, namely atebrin (mepacrine) was discovered, its structural formula was more like that of methylene blue than of quinine.

About that time Laveran and Mesnil had developed a technique for the transmission of trypanosomes from animal to animal in mice, and rats, and this allowed Ehrlich to continue his experimental enquiries under simpler conditions than the study of malaria allowed. Now he was easily able to note both the staining qualities of the parasites on the injection of dyes and also their number and degree of mobility. With this new technique, one of the first observations he made, in collaboration with Shiga, was the disappearance of trypanosomes from the blood of infected mice on the injection of a benzidine dye which they called trypan red. Although trypan red did not prove to be a success as a therapeutic agent in trypanosomiasis, it was the starting point of investigations which led ultimately to the discovery of the complicated organic compound known by the various names, Bayer 205, Germenin, Antrypol and its official B. P. name Suramin. This substance, although colourless, is related structurally to trypan red and has proved to be of great value in the treatment of trypanosomiasis (sleeping sickness). Later, French workers developed other dyes which killed trypanosomes *in vivo* including trypan blue and afridol violet. It might be well to remind you this point that the Gillman brothers in South Africa have recently shown that trypan blue injected into animals is capable of producing many of the tumours classed as reticuloses, including conditions closely resembling or possibly identical with

Hodgkin's disease and lymphosarcoma. This observation is not only a valuable contribution to knowledge of experimental cancer but it is a warning to investigators in chemotherapy that substances may have carcinogenic properties and other harmful effects as well as the particular curative action they are seeking. As regards afridol violet, although it did not prove to be of therapeutic interest, it contained the urea-linkage, which was found to be important in Bayer 205 (Suramin).

One other important landmark in chemotherapeutic advance demands reference, namely, the discovery made in 1905 by Thomas and Breinl in England that an organic derivative of arsenic acid, which had been marketed under the name of atoxyl, had a significant curative effect on trypanosome infections in small rodents. In 1907 Ehrlich discovered with Bertheim that 'atoxyl' was p-aminophenyl-arsenic acid and followed this up by showing in 1909 that, while it had but little visible effect on trypanosomes outside the body, when it was reduced to arsenoxide so that the pentavalent arenic became trivalent, the substance was rapidly lethal to trypanosomes in high dilutions. Continuing work on this subject and using spirochaetes as well as trypanosomes as biological test objects, he ultimately arrived, with Hata as his co-worker, at the greatest triumph in chemotherapy of that time namely the discovery of salvarsan (arsphenamine) as a curative agent in syphilis (1910). Salvarsan has for long been an enigma in its action. Ehrlich himself observed that it and its derivative neosalvarsan, when directly applied to spirochaetes did not impair their mobility or other signs of vitality, although arsenic is present in the molecule in the trivalent form. After such treatment, however, the organisms failed to produce infection when injected into other susceptible animals. Here again it seems likely that salvarsan has to be partially oxidised in the body to arsenoxide before it becomes powerfully lethal to spirochaetes and trypanosomes. On the other hand there is also the possibility that the action of arsphenamine is direct but eliminates these micro-organisms, not by killing them, but by suppressing their reproduction and multiplication.

I have gone into this early work of Ehrlich and his colleagues because it formed the stimulus and basis of all the later work, which we have witnessed. I shall not dwell, however, on the remarkable hypotheses of chemotherapeutic action that Ehrlich constantly propounded and developed during this period of fruitful experiment although these also played their part in subsequent work. It is, however, necessary to refer to his insistence on the supreme importance in work of this kind of establishing most clearly the relation of the minimal curative dose to the toxic dose in all drugs synthesised and tested biologically.

Sulphonamide and its derivatives:

I mentioned earlier that Ehrlich gave up the idea of relying on immunological reactions in the body when dealing with malaria and protozoal infections and turned to and developed what is now known as chemotherapy. In the case of the control of bacterial infections, on the other hand, immunology had had some signal triumphs and it was long thought that although chemotherapy had its place in the treatment of protozoal infections, it was not likely to be effective in infections due to bacteria. The first disproof, however, of this last view came when Morgenroth discovered that experimental pneumococcic infections in mice could be cured by optochin, an artificially produced homologue of quinine. It is true that this substance proved too toxic to man to be accepted as treatment for pneumonia, but the work raised the whole problem of the possible value of chemotherapy in the case of bacterial infections as well as in protozoal diseases.

Now the search for effective treatment against streptococcal infections in particular had been long and persistent and many scientists were beginning to despair of finding either immunological or chemotherapeutic remedy for such conditions when in 1935 Domagk published his finding that prontosil, a red sulphonamide of the dye chrysoidine, had a curative action on mice infected with streptococci. The Medical Research Council in England, of which I was at the time the administrative head, had several years previously established a unit of research to study puerperal sepsis and septicaemia under Dr. Colebrook. Thus the machinery for testing any therapeutic remedy in puerperal septicaemia was all ready for investigating the value of prontosil. Within a year of Domagk's publication, Colebrook and Kenny in London had reduced the mortality of puerperal septicaemia in their hospital at Hammersmith from 25% to 5%. This was the beginning of the sulphonamide story as a remarkable cure for streptococcal infections. While this clinical trial was in progress, Tréfouel, Nitti and Bovet in Paris had shown that sulphanilamide, a reduction-cleavage product of prontosil was as effective in experimental infections as prontosil itself; it was then found that prontosil undergoes this change to sulphanilamide in the body so that there was no further need to ascribe the curative action of prontosil to its properties as a dye. A further important observation was that sulphanilamide did not sterilize the culture in reasonable concentrations but only stopped the growth of the micro-organism; it was bacteriostatic rather than bactericidal. A further important development of this story was the preparation by Ewins and Phillips of the first derivative of sulphanilamide namely sulphapyridine, which had a specific curative effect in pneumococcal pneumonia, a discovery which opened up a new and important field of application of this form of chemotherapy. I shall not weary you with the further development of this subject, which is so familiar, nor with the production, mainly by pharmaceutical firms throughout the world, of such derivatives of sulphanilamide as sulpha-thiazole, sulphadiazine and sulphamezathine and many others, all of which products play their part in modern chemotherapeutic treatment and each of which seems to have some particular property as regards specificity or intensity of action or reduced toxicity to the host. It is a remarkable story of combined international action.

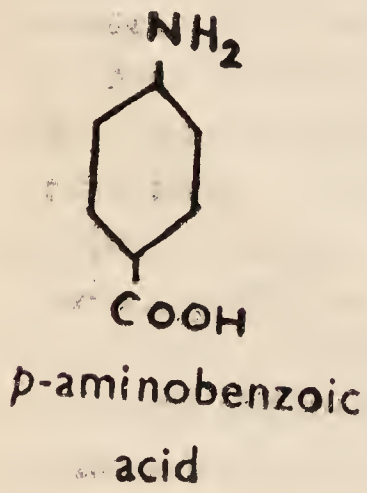
The Biochemical Action of Chemotherapeutic Substances:

The story of the sulphonamides as chemotherapeutic agents does not end with their great practical value in the treatment of infections, for their study has brought with it a hypothesis of the basis of their action in terms of cellular biochemistry, which has already proved of value not only to chemotherapy itself but to many other biochemical problems. The starting point of this kind of hypothesis had really been enunciated many years previously by v. Jancso, who attempted to deal with trypanosomes, not by killing them at once, but by depriving them of an essential nutriment, i.e., by starving them. He used for this purpose a diamidine, synthalin (decamethylene-diguanidine), which had been used previously as a synthetic substitute for insulin. He discovered that this substance caused the rapid disappearance of trypanosomes from the blood and assumed that these organisms had died because they were deprived of glucose. It is true that Warrington York disproved this conception, but v. Jancso's work not only had the merit of introducing a new mode of thought into possible chemotherapeutic activities, but also led to a useful and interesting study, by York and King, of other members of the diamidine group and brought to light stibamidine for the treatment of *kala-azar* and pentamidine, which

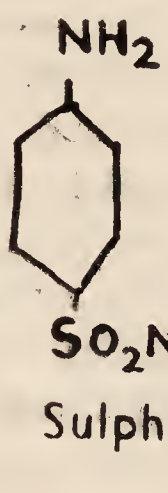
has proved effective in Babesia infections in dogs and in cattle.

Another biochemical hypothesis, which played its part in building up the modern conception of chemotherapeutic action, was that of Voegtlin, who regarded the action of arsenoxide produced in the body from arsphenamine and other curative arsenic derivatives as due to the arsenoxide radical combining with the thio radicals of glutathione in the cell protoplasm and thereby interfering with its respiratory mechanism. At a later stage, Fildes explained the disinfectant action of mercury salts on a similar basis, suggesting that the mercury ions combined with and inactivated the free thiol groups in bacteria and so suppressed their respiration.

With the development of the sulphonamides Fildes further advanced the hypothesis of a biochemical basis for chemotherapeutic action and assumed that these agents acted on some chemical mechanism necessary for the growth of the cell and so put out of action an 'essential metabolite' or a growth factor or an enzymic system. This hypothesis received support from the work of Stamp who found that a sterile extract of streptococci added to the culture medium, antagonised and neutralized the bacteriostatic effect of sulphanilamide on living bacteria. Finally, Woods, in Fildes's laboratory, found that an extract of yeast also antagonized the action of sulphanilamide and he proceeded to bring evidence to show that the cell constituent which had this action was probably p-aminobenzoic acid.



p-aminobenzoic acid



Sulphanilamide

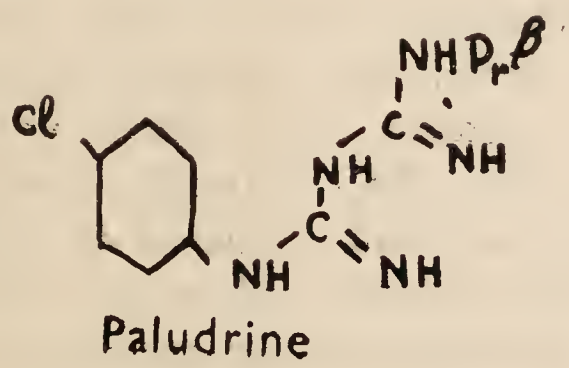
It will be seen that the structural formulae of p-aminobenzoic acid and sulphanilamide are closely similar. Woods suggested that sulphanilamide occupied the enzymic system normally taken by p-aminobenzoic acid and thereby deprived the cells of this essential metabolite. In support of his hypothesis, Woods found a fairly constant proportion between the concentration of sulphanilamide in a medium and the concentration of p-aminobenzoic acid necessary to neutralize its bacteriostatic effects: he also found that the concentration of p-aminobenzoic acid required to abolish the effects of different sulphonamide derivatives increased with their bacteriostatic activity. I shall not discuss further this subject of biochemical analogues, which has opened up many new fields of enquiry. I realize there are still difficulties to be overcome before the relation of p-aminobenzoic acid to sulphanilamide action can be fully accepted, not the least being the present inability to detect p-aminobenzoic acid itself in pathogens. There is, however, no longer any doubt that the main hypothesis of the antagonism of many biochemical analogues is a conception of fundamental importance in the biochemistry of the cell.

In the designing of structural analogues modelled to inhibit some essential life systems of bacteria, many factors have to be taken into consideration in order to retain in the inhibitor the power to participate in a required enzymic action, for instance Bell and Roblin and also Fildes and Rydon have demonstrated the importance of polar effects in bacterial inhibitors. Bell and Roblin, showed that sulphonamides in which the polarity of the SO_2 group approaches that of the COO ion of the p-aminobenzoic acid are the better inhibitors of those bacteria for which p-aminobenzoic acid is an essential metabolite.

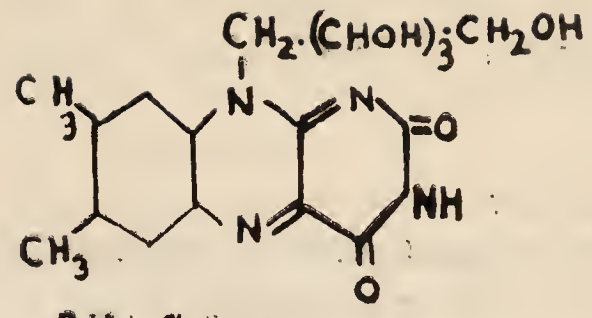
Sometimes the study of the metabolite itself leads to interesting information. Thus

the introduction of groups of known electro-polar properties into an essential metabolite, as for instance tryptophane, and the study of the effects of these products on growth promotion and inhibition may indicate the influence of the entering groups on the chemical affinity for the related enzyme or its ability to penetrate into the bacterial cell or its reactive centres of bio-attachment and their electro-polar characters in any active molecule. The results obtained from these studies on the metabolite can then be interpreted in terms of the chematherapeutic agents synthesised and tested.

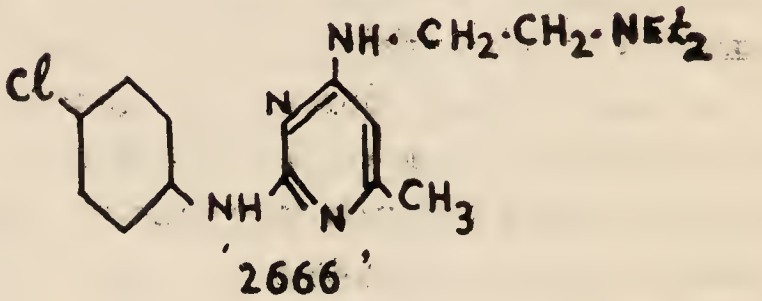
It is apparent that a chemo-therapeutic inhibitor may not even approach the geometry of a cell metabolite in detail so long as it carries the necessary reactive centres and the appropriate physical-effect groups. Thus, starting from substituted anilinopyrimidines, Curd and Rose built up a series of active inhibitors on the basis of altered structural relations till they discovered the well-known and, upto the present, the best anti-malarial paludrine. Though most compounds, which they synthesized and found active against malaria, showed anti-riboflavin activity, paludrine itself did not antagonize riboflavin just as it does not itself kill the malarial parasite. It will get interesting, however, to see whether the effective substance, to which it is converted in the body, when it is isolated and detected, will also have the anti-riboflavin effect. The difference between the molecular architecture of riboflavin and the active substituted anilinopyrimidines (code numbers 2666 and 3349) and paludrine with the retention of appropriate basicity can be seen in their respective formulae.



Paludrine



Riboflavin



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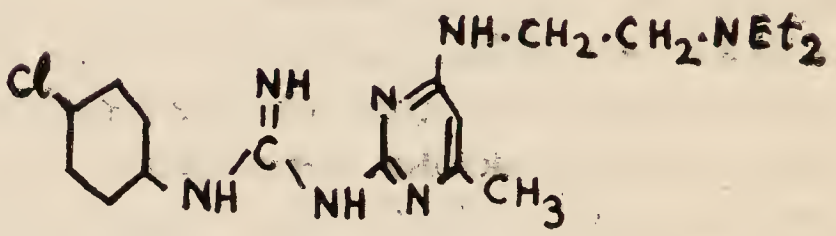

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Other examples of changes in molecular groupings of chemotherapeutic compounds which illustrate the dominant position held by polar properties can be seen in the replacement of the carboxyl group of acid metabolites by sulphonic acid or amide, or by a ketone. These forms of chemical changes have provided some useful inhibitors: thus Pyridine-3-sulfonic acid is related to nicotinic acid, pantoyl-taurine to pantothenic acid, p-amino-acetophenone to p-aminobenzoic acid and 3-acetylpyridine again to nicotinic acid.

This is only a very brief indication of some of the new principles and complexities underlying the building up of chemotherapeutic substances. Yet it is clear that good progress is being made in the study of the biochemical basis of chemotherapy although it is still necessary to synthesize and test many compounds before useful drugs of this kind can be discovered. It can be claimed, however, that important structural generalisations have now been established and it is largely because a therapeutic agent has to carry so many other essential qualities, such as suitable solubility, cell membrane perme-

ability and small toxicity to the host, that investigations of this kind remain very difficult.

Antibiotics:

Reference must now be made to the discovery of the remarkable series of antibiotic drugs made during the past ten years. Although sporadic instances of investigations based on this idea have occurred over a long period, these were generally ineffective until Dubos of New York cultured a soil bacillus under such conditions that it yielded certain polypeptides having a high toxicity for some pathogenic bacteria, one of them now called gramicidin having an intense destructive action on Gram-positive cocci. A more notable investigation, however, was that of Florey. He developed the original discovery of Fleming made in 1929 who had produced an extract of Penicillium Notatum which destroyed pathogenic cocci and the diphtheria group of bacilli but was inactive against Gram-negative organisms. Fleming had examined some of the properties of penicillin and had even considered some of its therapeutic possibilities but did not develop the subject further. Florey and his colleagues at Oxford, however, extracted the active principle from the culture fluid and purified it so as to be safe for intravenous administration. He then determined its curative properties in infected mice and finally crowned the whole work by producing complete evidence of its therapeutic qualities in man. Throughout this and earlier work I was in close touch with Florey and I wish to take this opportunity of saying that his work on penicillin was no mere chance. For years, to my knowledge, Florey had been interested in the defence of the body against pathogenic organisms and was inspired by the hope that it would be possible to find a natural substance which, while non-toxic to the body, would help its defence against pathogens. All his earlier work on the lymphatic system had this idea as its basis and it always seemed to me that there was a degree of natural justice in his establishment of penicillin as an antibiotic curative agent of remarkable power and low toxicity. His discovery was made in war time when the whole of British industry was occupied with essential war production so that it fell to the Americans to develop the large-scale production of penicillin for commercial purposes, a task which they accomplished with great enterprise and skill.

I should also like to refer to the fine international co-operation between British and American chemists during the late war, in their successful efforts to determine the chemical structure of penicillin and to their greater but unsuccessful efforts to affect its synthesis on a practical scale, although it is true that De Vigneaud succeeded in making a small quantity of this substance by artificial synthesis. Here is an instance, which is so often happening nowadays, in the study of the chemistry of biological products, where the chemist is learning new principles in organic chemistry as well as aiding medical science.

In more recent years, on the basis of Florey's technique other anti-biotics of very great importance have been discovered especially by American biologists and chemists. These new substances include streptomycin, chloromycetin, aureomycin and terramycin. This vast field of study is now too large for me to discuss here and it is only necessary to refer, in the first place, to the great advance in the treatment of tuberculosis that has resulted from the discovery of streptomycin, a substance which, for the first time in the history of man, is capable of curing a fair percentage of cases of miliary tuberculosis and tuberculous meningitis, types of tubercular infection from which patients previously always died. Secondly, I wish to refer to the successful treatment of typhoid fever by chloromycetin and to the curative effects of chloromycetin and aureomycin on

rickettsial infections including typhus fevers of various kinds and psittacosis. These last therapeutic discoveries have raised the hope that some day we will have at our disposal other antibiotic or chemotherapeutic substances which will cure such virus diseases as poliomyelitis, influenza and the common cold, infections which at present remain resistent to all forms of treatment.

In this rapid review of the remarkable development of drugs in the present century, I have omitted all reference to the discovery of new substances used as local anesthetics and analgesics and to the important new methods of procuring and controlling general anaesthesia that have been discovered since the days when chloroform, ether and nitrou oxide held complete sway. No branch of pharmacology and therapeutics seems to have escaped revolutionary changes. Nor have I discussed the new drugs used in malaria since the time when quinine was the sole anti-malarial at our disposal. Atebrin (mepacrine) as the first great improvement in anti-malarial treatment and this has now been followed by better drugs, such as paludrine (proguanil) and chloroquine. The discovery of the exo-erythrocytic form of the malarial parasite has brought enlightenment to our understanding of the action of anti-malarial substances. Paludrine has many advantages over the other drugs, because of its low toxicity to the host and because it destroys the exo-erythrocytic form of parasite, but it fails to prevent some relapses in Plasmodium Vivax infections, nor does it have large gametocidal properties.

The importance of leprosy in India also suggests that I should have spent more time in the consideration of new anti-leprosy drugs, the sulphones, but this discourse is already too long. I cannot, however, leave the subject of modern drug treatment without making a passing reference to a great difficulty which presents itself in many cases of chemotherapeutic and antibiotic treatment. I refer to drug resistance, which again and again develops and thwarts all the efforts of therapeutists. This seems to me a basic problem demanding investigation.

I have now completed my review of a subject, which continues and will continue on its victorious course—a course affecting the lives of all of us. No longer is it possible to deride the subject of therapeutics, although there are still important gaps to be filled even in the domain of infective disease, but these gaps are rapidly diminishing. There remains, however, one whole group of diseases which evade all investigation, both in their aetiological and therapeutic aspects. I refer to the degenerative diseases—cardio-vascular disease, rheumatic disease of all kinds, cancer and many other pathological changes that come with age. This is the next great task for preventive and curative therapy and recent results in this sphere are suggestive of ultimate success.